M1-1Scientific Abstract. Cardiovascular disease is the single leading cause of mortality in the United States, responsible for the deaths of two out of every five Americans, with a total of nearly 1 million deaths annually. Coronary artery disease describes a broad spectrum of ischemic syndromes that may evolve from atherosclerosis, thrombosis, and/or vasospasm. Current therapies include pharmacologic interventions and surgical therapy by mechanical revascularization using percutaneous transluminal coronary angioplasty or coronary artery bypass grafting. The identification of specific biologic mediators of angiogenesis make it possible to consider "therapeutic angiogenesis," where angiogenic molecules can be employed to develop new vascular networks to circumvent the ischemic consequences of atherosclerosis occluding the arterial system. The most specific of the known angiogenic indicators is vascular endothelial growth factor (VEGF). The focus of this protocol is to evaluate the adenovirus vector delivery of the human VEGF121 cDNA directly to ischemic myocardium of individuals with life threatening coronary artery disease. The vector to be used is Ad_{GV}VEGF121.10, an E1a$^-$, partial E1b$^-$, E3$^-$ based on the adenovirus 5 (Ad5) genome. This vector contains an expression cassette in the E1 region with the cytomegalovirus (CMV) promoter/enhancer controlling the VEGF121 cDNA. Three groups will be studied: two groups (A and C) that are undergoing coronary artery bypass grafting as part of their recommended treatment, and a compassionate use group (B) who have no alternative therapies available. In all groups, the Ad_{GV}VEGF121.10 vector will be administered directly to the ischemic myocardium at the time of open thoracotomy. Group A (n=9) is a dose ranging study to determine the highest safe dose to be used to Groups B and C. Group B will use that dose in a compassionate use group (n=10) and Group C will use that dose in a blinded, controlled (vs saline) study (n=20 vector, n=20 saline) superimposed on their usual therapy. All groups will be assessed with a variety of safety and efficacy parameters relevant to coronary artery disease. The following objectives will be met: (1) To determine the dose-dependent safety/toxicity of direct administration of the vector Ad_{GV}VEGF121.10 to the ischemic myocardium; and (2) To demonstrate whether direct administration of Ad_{GV}VEGF121.10 to the myocardium will induce growth of collateral blood vessels, improve coronary blood flow and improve cardiac function in the region of ischemia.